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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Samuel D. Bernal

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EXAMINER

EBRAHIM, NABILA G

ART UNIT

PAPER NUMBER

1618

MAIL DATE

DELIVERY MODE

06/23/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/019,494	Applicant(s) BERNAL ET AL.	
	Examiner NABILA EBRAHIM	Art Unit 1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 March 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2 and 11-21 is/are pending in the application.
- 4a) Of the above claim(s) 2 and 13-21 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The receipt of Applicant's amendments to the claims and remarks dated 12/23/2009 is acknowledged.

Status of Claims

Claims 1, 2, 11-21 are pending in the application.

Claims 3-10 were previously cancelled.

Claims 2 and 11-21 were withdrawn from consideration.

Claim 1 is under current examination.

Status of Office Action: Final

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. In view of amending the claims, the rejection of claim 1 under 35 U.S.C. 112, **first paragraph**, as failing to comply with the written description requirement is herein withdrawn.

2. In view of amending the claims, the rejection of claim 1 under 35 U.S.C. 112, **second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is herein withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. Claim 1 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Pomerantz Edwin WO 9726018 (Pomerantz) in view of Oseroff et al., Intramitochondrial Dyes Allow Selective in vitro Photolysis of Carcinoma Cells, PNAS, December 15, 1986, vol. 83, no. 24, 9729-9733 (hereinafter Oseroff) Copyright © 1986 by the National Academy of Sciences and further in view of Brenner, S. et al. Supravital staining of mitochondria with phenosafranin dyes, Biochim et Biophys.1953, pages 11480-11486. (Brenner). The claims remain rejected for the same reasons set forth in the office action dated 12/23/2008.

Response to Arguments

Applicant's arguments filed 3/25/2009 have been fully considered but they are not persuasive. Applicant argues that:

- Pomerantz teaches that dyes may cross the cellular membrane when they are fixed by agents known to disrupt the membrane; however, it does not necessarily hold that because of this, "the mitochondria as a subcellular structure would at least partially absorb the dye." Indeed, the Examiner recognizes that "Pomerantz did not disclose the specific retaining of the mitochondria to the dyes recited in instant claim 1 as amended".

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To respond: Pomerantz teaches the selective retaining of subcellular structures of the dye. Pomerantz combined with Oseroff disclose the same method using similar dyes to detect the same pathological cells in the same site (oral epithelium) and Oseroff discloses literally the selectiveness in the mechanism. Oseroff recites literally the selective marking of mitochondria.

- Examiner simply alleges that since the dyes as recited in claim 1 are cationic, they are obvious over Oseroff (and Pomerantz/Brenner), as it would be obvious to try using different cationic dyes to come up with the claimed invention.

To respond: The Examiner showed clearly that Oseroff teaches that carcinoma cell mitochondria preferentially accumulate and retain cationic dyes to a much greater extent than most normal cells. In addition, Oseroff teaches that rhodamine and cationic cyanine dyes were tested because they can potentially serve as targets for highly selective photochemotherapy. The Examiner indicated that alcian blue dye recited by Applicant in amended claim1 is a cationic cyanine dye. **The reference indicated that it is possible that other cationic molecules that concentrate within mitochondria at higher levels or that is more efficient photosensitizers will be still more effective.** Thus, Oseroff invited people having ordinary skill in the art to try other cationic cyanine dyes in this respect and since the rejection is under 35 U.S.C §103, an invitation to try is correct to reject the genus.

MPEP states that:

prior art reference that discloses a genus still does not inherently disclose all species within that broad category” but must be examined to see if a disclosure of the claimed

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species has been made or whether the prior art reference merely invites further experimentation to find the species.

- Applicant states that the Examiner recites on page 5 of the Office Action that "it is possible that other cationic molecules that concentrate within the mitochondria at higher levels will still be more effective."

To respond: this was not the Examiner opinion, this statement was disclosed by Oseroff (please see conclusion).

- It is not only the cationic nature of the dye that allows it to penetrate the mitochondria. For example, described on pages 9 and 10 of the specification are various mechanisms of entry into the mitochondria.

To respond: Applicant explains the different entries of the cationic dye to the mitochondria, however, instant specification teaches that the dyes recited in the instant claims are cationic (see abstract, pages 4, 5, 6, 7, 9, 10, 11, and Examples 1, 2, 3, 6, 7, and 8).

- Neither Pomerantz nor Oseroff teach nor suggest the claim element " the retention of said agent by the mitochondria of cancer cells in vivo which have been marked by absorption of said agent in the mitochondria thereof " as presently claimed. mitochondria Entry is affected by (i) the availability of the positive charge (i.e., as one skilled in the art knows, molecules could be folded and/or certain elements on the molecule could be masked, such as the positive charge itself); (2) the structure (and therefore identity) of the molecule (not simply that it is cationic) but other species/chemical groups on the molecule may bind to specific active sites, i.e., specific proteins, on the mitochondria; i.e., one skilled in the art knows that selective

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binding is not simply contingent upon charge; and (3) the hydrophobic/hydrophilic nature of the dye (once again, one skilled in the art knows that this is based upon the identity of the dye).

To respond: Oseroff teaches that carcinoma cell **mitochondria preferentially accumulate and retain certain cationic dyes** to a much greater extent than most normal cells. Thus, they can potentially serve as targets for highly selective photochemotherapy.

Oseroff also teaches that **positively charged lipophilic dyes can concentrate across membrane potentials into mitochondria; up to a 10,000-fold concentration gradient is theoretically possible**. Regarding the hydrophobic/hydrophilic nature of the dye, it is clear that the lipophilic dyes disclosed by Oseroff are hydrophobic. Finally, with regard to the underlined "in vivo" argued by Applicant, the title of Pomerantz invention is "METHODS AND COMPOSITIONS FOR IN-VIVO DETECTION OF ORAL CANCERS AND PRECANCEROUS CONDITIONS". Further, Oseroff also disclosed experimenting the dyes in vivo (see page 9730 forth paragraph).

- Applicant notes that Oseroff tests the following cancer cell lines: EJ bladder carcinoma cells, CX-i (human adenocarcinoma cell line), and the FaDu cell line (upper respiratory tract tumor - squamous cell line). As one skilled in the art knows, absorption and/or retention of various cationic dyes vary depending on cell type.

To respond: people having ordinary skill in the art are aware that epithelial cells are epithelial cells and cancers of epithelial cells are carcinomas regardless of the type of cell. Note that instant claims recite cancerous cells of the oral epithelium. The claims

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do not specify carcinoma or cell line. If Applicant's concern is as argued the variation of uptake depending on cell type, a histological document is attached to the Office Action as an evidence of the many types of cells in the epithelium of the oral epithelium (this includes all the types of epithelial cells in each of the lips, the tongue, the salivary gland and the pharynx) and Applicant is invited to show where in the instant specification the different types of epithelium and their response to different dyes are demonstrated.

- Oseroff does not teach or suggest "in the locus of normal cells" as presently claimed.

To respond: Oseroff does not have to teach each and every limitation of the instant claims since Pomerantz teaches that in-vivo diagnostic procedures for detection of premalignant oral lesions or oral carcinomas, employing dye compositions, which are selectively retained by tissues rendered abnormal due to dysplasia, hyperplasia, tumorigenesis, and other active surface lesions, are known in the art.

- Brenner discloses that "Although Janus Green B is widely used as a supravital stain for mitochondria there is no adequate theory to explain the mechanism of action. Janus green B is diethylphenosafraninaxzodimethylaniline and Cowdry demonstrated that diethylsafranin itself, as well as other dyes containing it, stained mitochondria supravitaly. Because dimethylphenosafranin and its derivatives failed to give the selective supravital staining reaction, Cowdry claimed that the specificity of Janus green B depends on the diethylphenosafranin part of the molecule alkyl substitution on an amino group attached to the aromatic ring increases the positivity of the nitrogen atom and ethyl groups exert a stronger effect than methyl groups than methyl groups.

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Thus the diethylphenosafranins would be expected to be more basic than the dimethylphenosafranins and this difference between the two types of dyes might be related to the staining specificity.

To respond: phenosafranin was disclosed generically in the instant specification once. No further specific type, formula for the compound or description was disclosed. Thus, the janus green B (diethylsafranin is a species derived from the genus phenosafranin taught by instant application) is a species which reads on the generic disclosure.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

/Nabila Ebrahim/

Examiner, Art Unit 1618

/Michael G. Hartley/

Supervisory Patent Examiner, Art Unit 1618

